



4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2011-D-0376]

Dietary Supplements: New Dietary Ingredient Notifications and Related Issues; Revised Draft Guidance for Industry; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice of availability.

SUMMARY: The Food and Drug Administration (FDA or we) is announcing the issuance of a revised draft guidance for industry entitled "Dietary Supplements: New Dietary Ingredient Notifications and Related Issues." The revised draft guidance supersedes FDA's July 2011 draft guidance on the same topic. The revised draft guidance, when finalized, will help industry in evaluating whether to submit a premarket safety notification for a new dietary ingredient (NDI), or for a dietary supplement containing an NDI, and in preparing such premarket safety notifications (also referred to as NDI notifications).

DATES: Although you may comment on any guidance at any time (see 21 CFR 10.115(g)(5)), to ensure that FDA considers your comment on the draft guidance before we begin work on the final version of the guidance, submit either electronic or written comments on the draft guidance by [INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL REGISTER].

ADDRESSES: You may submit comments as follows:

Electronic Submissions

Submit electronic comments in the following way:

- Federal eRulemaking Portal: <http://www.regulations.gov>. Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to <http://www.regulations.gov> will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on <http://www.regulations.gov>.
- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see "Written/Paper Submissions" and "Instructions").

Written/Paper Submissions

Submit written/paper submissions as follows:

- Mail/Hand delivery/Courier (for written/paper submissions): Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.
- For written/paper comments submitted to the Division of Dockets Management, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in "Instructions."

Instructions: All submissions received must include the Docket No. FDA-2011-D-0376 for "Dietary Supplements: New Dietary Ingredient Notifications and Related Issues; Revised Draft Guidance for Industry." Received comments will be placed in the docket and, except for those submitted as "Confidential Submissions," publicly viewable at <http://www.regulations.gov> or at the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

- Confidential Submissions--To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states "THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION." The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on <http://www.regulations.gov>. Submit both copies to the Division of Dockets Management. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as "confidential." Any information marked as "confidential" will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA's posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at: <http://www.fda.gov/regulatoryinformation/dockets/default.htm>.

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to <http://www.regulations.gov> and insert the docket number, found in brackets in the heading of this document, into the "Search" box and follow the prompts and/or go to the Division of Dockets Management, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

Submit written requests for single copies of the draft guidance to the Division of Dietary Supplement Programs, Center for Food Safety and Applied Nutrition (HFS-810), Food and Drug Administration, 5001 Campus Drive, College Park, MD 20740. Send one self-addressed adhesive label to assist that office in processing your requests. See the SUPPLEMENTARY INFORMATION section for electronic access to the draft guidance.

FOR FURTHER INFORMATION CONTACT: Ali Abdel-Rahman, Center for Food Safety and Applied Nutrition (HFS-810), Food and Drug Administration, 5001 Campus Dr., College Park, MD 20740, 240-402-1853.

SUPPLEMENTARY INFORMATION:

I. Background

We are announcing the availability of a revised draft guidance for industry entitled "Dietary Supplements: New Dietary Ingredient Notifications and Related Issues." This draft guidance supersedes the July 2011 draft guidance on this topic (76 FR 39111; July 5, 2011) and is being issued consistent with our good guidance practices regulation (21 CFR 10.115). The draft guidance, when finalized, will represent our current thinking on this topic. It will not create or confer any rights for or on any person and will not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations.

On October 25, 1994, the Dietary Supplement Health and Education Act of 1994 (DSHEA) (Pub. L. 103-417) was signed into law. DSHEA amended the Federal Food, Drug, and Cosmetic Act (the FD&C Act) by adding, among other provisions: (1) Section 201(ff) (21 U.S.C. 321(ff)), which defines the term "dietary supplement" and (2) section 413 (21 U.S.C. 350b), which describes requirements for NDIs. Among other things, section 413 of the FD&C Act requires the manufacturer or distributor of an NDI, or of a dietary supplement containing the NDI, to submit a premarket notification to FDA (as delegate for the Secretary of Health and Human Services) at least 75 days before introducing the NDI or dietary supplement into interstate commerce, unless the NDI and any other ingredients in the dietary supplement have been present in the food supply as an article used for food in a form in which the food has not been chemically altered (21 U.S.C. 350b(a)(1)). The notification must contain the information, including any citation to published articles, which is the manufacturer or distributor's basis for concluding that a dietary supplement containing the NDI will reasonably be expected to be safe.

This draft guidance has several purposes. First, it is intended to help dietary supplement manufacturers and distributors decide whether to submit an NDI notification. In addition, the draft guidance is intended to provide recommendations on how to conduct a safety assessment for an NDI notification and what to include in the notification. In question and answer form, the draft guidance presents FDA's views on what qualifies as an NDI; when an NDI notification is required; the procedures for submitting an NDI notification; the types of data and information that manufacturers and distributors should consider when evaluating the safety of a dietary supplement containing an NDI; and what should be included in an NDI notification. In addition, the draft guidance contains questions and answers about parts of the dietary supplement

definition (section 201(ff) of the FD&C Act) that can affect whether a particular substance may be marketed as a dietary ingredient in a dietary supplement.

We issued the original version of this draft guidance in the Federal Register of July 5, 2011 (the 2011 draft guidance). We gave interested parties an opportunity to submit comments by October 3, 2011. In the Federal Register of September 9, 2011 (76 FR 55927), we extended the comment period to December 2, 2011. We received numerous comments on the 2011 draft guidance.

Based on those comments and on meetings with industry and other stakeholders, we realized that the 2011 draft guidance contained gaps and unclear statements that were subject to confusion and misinterpretation. Therefore, we decided to clarify and better explain our thinking on some critical issues, in addition to explaining their public health significance, and to request additional comments on these issues before publishing a final guidance. We have revised certain questions and answers and added a number of new questions and answers.

The major topics on which we have revised or added questions and answers are as follows:

- Chemical alteration--Dietary supplements containing an NDI are exempt from the notification requirement when they contain only dietary ingredients that have been present in the food supply as an article used for food in a form in which the food has not been chemically altered. Section IV.B of the revised draft guidance explains FDA's interpretation of "present in the food supply as an article used for food" and the public health basis for that interpretation. In addition, section IV.B has been revised to address the question of what constitutes "chemical alteration" more fully and to explain FDA's reasoning on this issue, as well as discussing additional examples of when chemical

alteration occurs and when it does not. Because no guidance document can cover every possible manufacturing scenario, the draft guidance encourages industry to consult with FDA in advance on such matters.

- Manufacturing changes that create an NDI--A related issue addressed in section IV.A of the draft guidance is when a manufacturing change alters the structure or properties of an ingredient and creates an NDI for which a notification must be submitted. The revised draft guidance provides examples of manufacturing changes that alter the identity of the ingredient, the key factor in determining whether they also change the regulatory status of the ingredient.
- Synthetic substances--Section IV.D of the revised draft guidance contains an expanded discussion clarifying FDA's views on when synthetic copies of botanical and other dietary ingredients qualify as dietary ingredients under the FD&C Act. FDA's thinking is based on the text of section 201(ff)(1) of the FD&C Act, which defines some types of dietary ingredients by identity and others by function.
- New dietary ingredient definition and list of "grandfathered" dietary ingredients--In section IV.A of the draft guidance, we revised our response to the question about whether there is an authoritative list of dietary ingredients marketed before October 15, 1994 (a so-called "grandfathered list" or "old dietary ingredient list"). Dietary ingredients marketed before that date are not NDIs and therefore are not subject to the premarket notification requirement in section 413 of the FD&C Act. Although there is currently no authoritative list of "grandfathered" ingredients, the revised answer notes that FDA is prepared to compile such a list based on independent and verifiable data to be submitted by industry. The revised answer also discusses FDA's thinking on the regulatory status of

dietary ingredients that would be on such a list, as well as the status of dietary ingredients not on such a list.

We also revised several questions and answers in section IV.A to clarify various matters regarding FDA's interpretation of the terms "marketed" and "dietary ingredient" in section 413(d) of the FD&C Act, which defines an NDI as a dietary ingredient that was not marketed in the United States before October 15, 1994, and we added more examples of documentation that can be used to show that a dietary ingredient was marketed prior to October 15, 1994.

- Structuring notifications efficiently and relying on data from prior notifications and master files--We added several questions and answers in section IV.C of this draft guidance to suggest ways manufacturers and distributors can reduce the number of NDI notifications they must file and to clarify when data and information from a previous notification or "master file" may be used in a notification. For example, the answer to a new question clarifies that firms may submit an NDI notification that covers the use of the NDI in multiple dietary supplements and includes safety data for a range of doses and/or differing conditions of use. This answer also explains that a firm may submit a confidential "master file" containing specifications, manufacturing procedures, and other identity information for an NDI, and may incorporate information from the master file into its own NDI notification or may authorize another firm to rely on information from the master file in a notification for a dietary supplement containing the NDI. We also added a question and answer to describe when a firm may rely on data in another notification. In addition, section IV.C now includes a question and answer with six examples distinguishing situations in which separate notifications are required for

different dietary supplements containing the same NDI from situations in which a single NDI notification covers multiple dietary supplements containing the same NDI. Finally, section IV.C now clarifies that, although a combination of NDIs is itself an NDI, a combination of grandfathered dietary ingredients is not, even if that combination has not been used in a dietary supplement before.

- Identity information to include in an NDI notification--We revised several questions and answers in section VI.A in consideration of comments regarding chemical and botanical information necessary to determine the identity of an NDI. We also added a new question and answer with recommendations about what chemistry information should be included in a notification for an enzyme NDI. In addition, since some of the standard references on nomenclature of plants and microorganisms have been renamed or updated since the 2011 draft guidance, we updated the citations to refer to the most recent edition.
- Electronic submission--We updated the question and answer in section V.A about electronic submission of NDI notifications. The updated answer states that we are accepting NDI notifications electronically and provides the Internet address for the electronic submission gateway. As before, the answer notes that firms still have the option to submit paper notifications to FDA using the procedure described in 21 CFR 190.6.
- PDF form for NDI notifications submitted on paper--Because our electronic submission gateway for NDI notifications is now available, we have decided not to provide a competing form for paper notifications. Therefore, we have removed "Appendix B: 75-Day Pre-Market New Dietary Ingredient Notification Form" from the draft guidance.

- Safety information to include in an NDI notification--We revised several questions and answers in sections VI.B and VI.C to clarify our thinking on compiling and evaluating scientific evidence about the safety of NDIs and dietary supplements that contain NDIs. In section VI.B, we clarified our thinking on the use of foreign history of use data. We also added a recommendation to consult "Principles and Methods for the Risk Assessment of Chemicals in Food," a joint publication of the World Health Organization and the Food and Agriculture Organization of the United Nations, as a useful source of information on conducting human clinical studies for NDIs and dietary supplements. In response to comments, we removed all references to FDA's "Redbook" guidance, which contains recommendations on toxicity studies and other scientific evidence needed to determine the safety of food additives. We also revised section VI.B to explain that the NDI safety standard is different from the standards for other FDA-regulated products and clarify that evidence for an NDI safety evaluation should be compiled to meet that standard. Although the revised draft guidance no longer cites the Redbook, we continue to recommend the use of the dietary exposure assessment methodology and some toxicology tests that are also used for the evaluation of food additives because these are standard scientific methods not specific to any particular safety assessment paradigm. Finally, we added a new question at the end of section VI.C to emphasize that this draft guidance contains recommendations about safety information to include in an NDI notification, but these recommendations are not requirements.
- Other changes--We made clarifying changes, explanatory changes, and editorial changes throughout the document. We also updated references and links and added new references where appropriate.

II. Paperwork Reduction Act of 1995

Under the Paperwork Reduction Act of 1995 (the PRA) (44 U.S.C. 3501-3520), Federal agencies must obtain approval from the Office of Management and Budget (OMB) for each collection of information they conduct or sponsor. This draft guidance contains proposed collections of information. "Collection of information" is defined in 44 U.S.C. 3502(3) and 5 CFR 1320.3(c) and includes Agency requests or requirements that members of the public submit reports, keep records, or provide information to a third party. Section 3506(c)(2)(A) of the PRA (44 U.S.C. 3506(c)(2)(A)) requires Federal Agencies to publish a 60-day notice in the Federal Register soliciting public comment on each proposed collection of information before submitting the collection to OMB for approval. To comply with this requirement, we intend to publish a 60-day notice on the proposed collections of information in this draft guidance in a future issue of the Federal Register.

This draft guidance also refers to previously approved collections of information found in FDA regulations. These collections of information are subject to review by OMB under the PRA. The collections of information in 21 CFR part 111 have been approved under OMB control number 0901-0606, and the collections of information in § 190.6 have been approved under OMB control number 0910-0330.

III. Other Issues for Consideration

Although FDA welcomes comments on any aspect of this draft guidance, we particularly invite comment on the following:

- What processes alter the identity of an ingredient marketed prior to October 15, 1994, and thus create an NDI? We are especially interested in recommendations for clearer

examples or criteria to differentiate changes in manufacturing methods and starting materials that alter the identity of the ingredient from changes that do not.

- What processes "chemically alter" an ingredient within the meaning of section 413(a)(1) of the FD&C Act, and why? Conversely, what processes do not cause chemical alteration, and why? Are there certain processes, such as tinctures, that sometimes result in chemical alteration and sometimes do not? What criteria should be used to evaluate whether an ingredient has been chemically altered? We are especially interested in receiving scientific information that shows whether a particular process actually results in chemical alteration.
- What method of compiling independent and verifiable data on the marketing of dietary ingredients before October 15, 1994, would be most effective? How should an authoritative list of "grandfathered" ingredients based on such data be developed and implemented?

As FDA considers the development of final guidance, we will review comments received on this revised version, as well as comments on the 2011 draft guidance that are still relevant.

IV. Electronic Access

Persons with access to the Internet may obtain the guidance at either <http://www.fda.gov/FoodGuidances> or <http://www.regulations.gov>. Use the FDA Web site listed in the previous sentence to find the most current version of the draft guidance.

V. References

The following references are on display in the Division of Dockets Management (see ADDRESSES) and are available for viewing by interested persons between 9 a.m. and 4 p.m., Monday through Friday; they are also available electronically at <http://www.regulations.gov>.

FDA has verified the Web site addresses, as of the date this document publishes in the Federal Register, but Web sites are subject to change over time.

1. International Programme on Chemical Safety, "Principles and Methods for the Risk Assessment of Chemicals in Food," Environmental Health Criteria 240 (2009), available at: <http://www.who.int/foodsafety/publications/chemical-food/en/>.

2. The official name of the Redbook is "Guidance for Industry and Other Stakeholders: Toxicological Principles for the Safety Assessment of Food Ingredients," available at:
<http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/IngredientsAdditivesGRASPackaging/ucm2006826.htm>.

Dated: August 9, 2016.

Jeremy Sharp,

Deputy Commissioner for Policy, Planning, Legislation, and Analysis.

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